Antisoma

3270 '99 SEP 17

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fischers Lane rm 1061
Rockville
Md 20852
USA

16 September 1999

Dear Sir

Docket Number 99D-2096

Please find enclosed comments on the Guidance for Industry 'Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations'. The comments are divided into Comments on Scientific Content, Discussion Points and a Proposal for Remit of Orphan Status Protection.

1 Comments on Scientific Content

Section II Background and Section III Scope

It is correctly stated in Section II that the V_H and V_L regions form the antigen binding site of the molecule. However, under Section III it is said that the CDRs form the antigen binding site. The latter is incorrect as the CDRs combined with the framework regions form the V_H and V_L ie the antigen binding site.

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Under Section II it is stated in the last paragraph that because of antibody diversity it is unlikely that independently derived monoclonal antibodies with the same antigen specificity will have the same amino acid sequences. Many antigens are now cloned and epitope mapped, therefore, it may be possible to immunise mice of the same strain using a restricted epitope and derive an antibody, which had the same amino acid sequence.

Section IV Interpreting Sameness for Monoclonal Antibody Products

A Structural Features of Antibodies

The second sentence states that the variable region is divided into 3 CDRs and 3 FRs in fact there are 3 CDRs and 4 FRs.

The proposed interpretation of sameness is of worry as the term minor amino acid differences is not defined.

2 Discussion Points

Section IV Interpretation of sameness for Monoclonal Antibody Products

B Sameness for Naked Monoclonal Antibody Products

This section states *"For the purpose of determining sameness of naked monoclonal antibodies under the Orphan Drug Act the complementarity determining regions of the heavy and light chain variable regions will be viewed by the FDA as the principal molecular structural feature of a monoclonal antibody product. .....The proposed interpretation of sameness for two monoclonal antibody drugs would be considered the same if the amino acid sequences of the complementarity determining regions were the same or there were only minor amino acid differences between them. Other potentially important amino acid differences outside the complementarity determining regions, or differences due to glycosylation patterns or post translational modifications would not per se*

cause the products to be considered different unless the subsequent drug was shown to be clinically superior."

Our Interpretation of the guidelines on sameness for Monoclonal Antibody Products is that molecules would not be protected by Orphan Drug Status which have slightly different sequences within the binding region, but do have essentially the same biological function.

- The sequence of an antibody with orphan drug status could be determined and sequences altered without altering specificity. For example, when the gene encoding an antigen is identified and the sequence of that gene product is known epitopes shown to be immunodominant could be used to generate many antibodies of identical specificity all with slightly different V_H and V_L sequences. This is known to occur for antibodies against tumour associated antigens such as CEA and the MUC-1 gene product which is only 20 amino-acids tandemly repeated to form the PEM core protein. An example of the above can be found in Immunology by Ivan Roitt, et al, 1985 published by Church Livingston. Another example of alteration of gene sequence without altering specificity is if a competitor company determined the sequence of an antibody with orphan drug status and simply shuffled the V_L genes, where only the V_H domain is responsible for binding or by introducing small changes by site-directed mutagenesis.

Section IV C Sameness for Antibody conjugates, Fusion proteins, and Bispecific Antibodies

Paragraph 2, sentence 3, states that *"conversely, two monoclonal antibody conjugates or fusion proteins would be determined to be the same if both the CDR sequences of the antibody and the functional element of the conjugate molecule were the same"*. If the framework regions were different or if the chemical chelate binding the functional element were different, would these be regarded as being the same? For example, it would also be possible to modify

the chemical chelate without altering the function of the product, and therefore evade orphan drug status protection.

3 Proposal for Remit of Orphan Status Protection

Based on the above discussion points our comment on the draft guidelines would be to allow the remit of Orphan Status Protection to include an element of functionality. That is when an antibody is against the same target antigen and has the same effector it should be regarded as being the same for orphan drug purposes irrespective of the binding site sequence of the antibody.

If you would like any clarification on these comments, please do not hesitate to contact the undersigned (tel; +44 181 799 8228; fax: +44 181 799 8201; email: rachel.adams@antisoma.co.uk).

Yours sincerely

Rachel Adams

Dr Rachel Adams
Head of Regulatory Affairs

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